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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,336	JOLIVET ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15, and 17-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the action mailed 09/11/07 is withdrawn. This is a non-final action. In view of the withdrawal of the finality of the action mailed 9/11/07, applicant's Appeal Brief, received 07/11/08, is rendered moot.

Status of the Claims

Claims 1, 3-15, and 17-60 are currently pending in this application.

Appeal Brief

Applicant's arguments/remarks set forth in the Response, received 01/11/08, and in the Appeal Brief, filed 07/11/08, have been considered. However, as stated above, this Office action renders the appeal brief moot.

Response to applicant's arguments/remarks

Obviousness-Type Double Patenting Rejection (claims 1, 3-15, and 17-60)

These rejection are withdrawn.

Rejection under 35 USC 112, second paragraph (claims 1, 3-15, and 17-60)

This rejection is withdrawn.

Rejection under 103(a) (claims 1, 3-15, 17-60)

This rejection is withdrawn.

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-15, and 17-60, are rejected under U.S.C. 103(a) as being unpatentable over De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only), in view of Lokich et al., in further view of Chu et al. (US Patent 5,817,667).

Claim 1 recites "[a] method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least

72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 p.M is achieved during the administration, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma." Claim 8 recites "[a] method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0 laM, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma." Claim 13 recites "[a] method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m2/day, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma." Claim 23 recites "wherein said continuous infusion is administered for a period of 3 to 7 days." Claim 33 recites "further comprising repeating said continuous infusion at an interval of every 4 weeks." Claim 37 recites "wherein said method further comprises, in combination with said

continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers." Claim 39 recites "wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833." Claim 43 recites "wherein said troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially." Claim 44 recites "wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously." Claim 45 recites "wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations." Claims 46 recites "wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations." Claim 47 recites "[a] method for the administration of troxacitabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction." Claim 56 recites "[a] method according to claim 13, wherein said method further comprises, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

De Bono et al. disclose pharmacokinetic and pharmacodynamic results of troxacitabine in thirty-nine patients with advanced solid malignancies wherein said troxacitbabine was given at eight dose levels ranging from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days. De Bono et al. teach that the pharmacokinetics of troxacitabine is dose-independent wherein the mean (SD) values for the volume of distribution at steady-state and clearance (Cl) were 60 (32 L and 161 (33) ml/min, respectively, on day 1. After treatment on the fifth day, terminal half-life values averaged 39 (63) hours, and Cl, was reduced by approximately 20%, averaging 127 (27) ml/min. The principal mode of drug elimination was renal. A patient with metastatic ocular melanoma experienced a partial response. De Bono et al. further suggest that broad disease-directed evaluations of troxacitabine as a 30-minute infusion daily for 5 days every 4 weeks at a dose of 1.5 - 1.2 mg/m2/day, and possibly less frequent schedules, were warranted. Clearly, De Bono et al. teach a method for treating patients with solid malignancies, including ocular melanoma, comprising administering an effective amount of troxacitabine via a 30-min intravenous infusion for a period of 120 hours (5 days) wherein a steady state plasma concentration of troxacitabine was achieved during the administration. De Bono et al. disclose that a patient with melanoma experienced a partial response is evidence that the dose range from 0.12 to 1.8 mg/m2/day via a 30-min intravenous infusion for five days is a therapeutically effective amount of troxacitabine. Although De Bono et al. teach solid maliganancies, this reference does not teach the instant cancers recited in claim 1. Also, De Bono et al. do not teach continuous infusion for a period of at least 72 hours wherein a steady

state plasma concentration of troxacitabine of 0.03 to 2.0 μM achieved during the administration.

Lokich et al. is added to show the general state of the art regarding continuous infusions of antineopastic drugs. Lokich et al. teach that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days. Lokich et al. teach that the rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure; the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak levels (page 15, col. 1, introduction section, lines 8-15; see also page 18, Table 3). Lokich et al. teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (page 15, col. 1, line 15 to col. 2, line 3). Lokich et al. also teach that the selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects; the dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy (page 15, col. 2, lines 3-10). Lokich et al. teach that for some agents, cumulative effects with infusional

administration may result in accentuated toxicity necessitating adjustments in the dose rate in order to permit long term administration for weeks or even months (page 23, lines 3-8). Lokich et al suggest that conceptually longer duration infusions permit a protracted exposure to the neoplastic cell optimizing the potential for a drug-cell interaction (page 23, col. 1, lines 8-18).

Chu et al. (US Patent 5,817,667) teach a method for treatment of cancer in humans and other host animals comprising administering an effective amount of troxacitabine (column 3, lines 21-52). Chu et al. specifically teach that various cancer cells lines are sensitive to troxacitabine, including leukemia, lymphoma, prostate, bladder, lung, colorectal, breast, pancreas, liver, ovarian cancers (see Figure 4). Chu et al. teach that humans, equines, canines, bovines and other animals, and in particular, mammals, suffering from cancer can be treated by administering to the patient an effective amount of (-)-OddC (i.e. troxacitabine) or a pharmaceutically acceptable salt thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known anticancer or pharmaceutical agents; this treatment can also be administered in conjunction with other conventional cancer therapies, such as radiation treatment or surgery (col. 10, lines 50-59). Chu et al. also disclose that troxacitabine is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30mM, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient (cols. 10-11, Example 8, see especially col. 11, lines 13-19). Chu et al. teach alkylating agents (e.g. nitrogen mustards,

ethyleneimine compounds, alkyl sulfates, cisplatin); antimetablistes; nucleoside derivatives (e.g. 5-fluorouracil); nucleoside analog of dexocytidine (e.g. cytosine arabinoside); cytidine analog (e.g. 5-azacytidine); 2-fluoroadenoside-5'-phosphate (Fludarabine); anthracyclines; hormomal agents ; natural products and their derivatives; 2-chlorodeoxyadenosine(col. 2, line 7 to col. 3, line 10).

It would have been obvious to a person of skill in the art at the time the invention was made to modify the 30-minute infusion rate of troxacitabine as taught by De Bono et al. by increasing the duration of infusion as taught by Lokcih et al. in order to administer the troxacitbine via a continuous infusion for a period of at least 72 hours to minimize troxacitbine-associated adverse effects. One would have been motivated to modify the infusion duration to minimize troxacitabine adverse effects using continuous infusion of at least 72 hours because Lockich et al. suggest that cumulative effects of infusional administration may result in accentuated toxicity which may require adjustments in the dose rate in order to permit long term administration of the drug for weeks or even months. Besides, Lockich et al. disclose that conceptually longer duration infusions permit a protracted exposure of the antineoplastic agent to the neoplastic cell, which optimizes the potential for a drug-cell interaction. Also, it would have been obvious to a person of skill in the art at the time the invention was made to administer troxacitabine via continuous infusion over a period of at least 72 hours to achieve any measurable troxacitabine drug level in plasma, including a maxmimum plasma concentration of 0.03 to 2.0 μM by modifying the infusion rate as taught by Lokich et al. in order to provide a therapeutically effective amount of troxacitabine in the

blood for its therapeutic effects. One would have been motivated to administer troxacitabine via continuous infusion over a period of at least 72 hours to achieve any measurable troxacitabine drug level in plasma, including a maxmimum plasma concentration of 0.03 to 2.0 μM by modifying the infusion rate, because De Bono et al. impliedly teach a method for monitoring troxacitabine levels in the plasma/blood. Further, it would have been obvious to a person of skill in the art at the time the invention was to treat a patient with cancer (e.g. lung cancer, prostate cancer) as taught by Chu et al. by administering troxacitabine via a continuous infusion for a period of at least 72 hours to achieve a targeted plasma concentration of troxacitabine, including a maximum plasma concentration of 0.03 to 2.0 μM during the administration of troxacitabine, because Chu et al. suggest a method for treating cancer (e.g. prostate cancer, lung cancer) with troxacitabine, wherein troxacitbine is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30mM, which overlap with the instant claimed troxacitabine plasma levels. One would have expected to successfully treat a patient with cancer (e.g. lung cancer or prostate cancer) by administering troxacitabine via a continuous infusion for a period of at least 72 hours to achieve a targeted plasma concentration of troxacitabine, including a maximum plasma concentration of 0.03 to 2.0 μM during the administration of troxacitabine because both De Bono et al. and Lokich et al. are concerned with administration of antineoplastic drugs via infusion and both De Bono et al. and Chu et al. teach methods of treating solid cancers comprising administerng troxacitabine in dosage amounts that are effective for treating cancer, while Chu et al. teach solid

cancers (e.g. lung cancer, prostate cancer, leukemia, lymphoma) which overlap with the instant cancers recited in claim 1.

The limitations regarding the sequential, separate, combined, or simultaneous administration of a second agent or additional agents are routine in the oncology art and are reasonably construed to be within the skill and knowledge of an artisan skilled in the art. It is also the examiner's position that it is routine in the pharmaceutical art to use pharmacokinetic data such as terminal half-life, clearance, and area under the curve (AUC), to modify the infusion rate and/or dose to achieve a desirable steady state plasma level of a drug.

Thus, it would have been obvious to a person of skill in art to at the time the invention was made to create the instant claimed invention with reasonable predictability.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-15, and 17-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 9, 10, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, 31, 32, 33, 34, 35, and 36 of U.S. Patent 6,630,480 (Gourdeau '480), in view of De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only) and Lokich et al., in further view of Chu et al. (US patent 5,817,667).

In particular, claim 1 of Gordeau '480 recites a method for treating a patient with leukemia comprising administering to said patient having chronic myelogenous leukemia or acute myelogenous leukemia, a therapeutically effective amount of a compound having "formula I." Unlike the claims of the instant application (i.e. claims 1,

3-15, and 17-60), the reference claims do not disclose the limitations of a continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration.

The above discussions of De Bono et al., Lokich et al., and Chu et al. are incorporated by reference.

It would have been obvious to a person of skill in the art to modify the reference method of treatment to incorporate the teachings of the prior art with respect to infusion duration, plasma drug concentration, dosing interval, and frequency of dosing to minimize the adverse effects associated with troxacitabine administration. One would have been motivated to incorporate said teachings because the reference claims, De Beno et al, and Chu et al. are al. directed to methods of treatment of cancer comprising administering troxacitabine and Debono et al. and Lokich et al. are directed to infusion of anti-cancer drugs. Thus, the reference claims are deemed to be obvious variants of the instant claims for the above reasons.

In addition, claims 1, 3-15, and 17-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 11-21 of copending Application No. 10/824,563 in view of in view of De Bono et al. (J. Clin. Oncol. 2002: 20(1): 96-109, abstract only) and Lokich et al., in further view of Chu et al. (US patent 5,817,667).

In particular, reference claim 11 is directed to a method for treating leukemia comprising administering troxacitabine in combination with a second agent. Unlike the instant claims, the reference claims do not disclose the limitations of a continuous

infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration. The above discussions of De Bono et al, Lokich et al, and Chi et al. are incorporated by reference. However, it would have been obvious to a person of skill in art to modify the reference method to minimize the side effects of troxacitabine for the reasons discussed above in connection with the rejection relating to issued patent '480. One would have been motivated to modify the reference method of treatment to minimize side effects because reference claims, De Beno et al, and Chu et al. are al. directed to methods of treatment of cancer comprising administering troxacitabine and Debono et al. and Lokich et al. are directed to infusion of anti-cancer drugs. Thus, the reference claims are deemed to be obvious variants of the instant claims for the above reasons.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending applications have not in fact been patented.

Relevant Art of Record

The post-dated cited art made of record and relied upon is considered pertinent to applicant's invention.

Benet LZ et al. (Benet et al. Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination. In, Goodman & Gilmans: The Pharmacological Basis of Therapeutics, 9th edition (1996): page 18) teach that Clinical Pharmacokinetics attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentration of drugs in biological fluids (page 18, column 1, lines 2-6). Benet LZ et al. further teach that the

various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters and that the three most important parameters are clearance, volume of distribution, and bioavailability; of lesser importance are the rates of availability and distribution of the agent (page 18, column 1, lines 10-19).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the

automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12 September 2008

/C. R./

Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611